NICE National Institute for Health and Care Excellence

Slides for public

Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in adults with elevated triglycerides

Chair's presentation

Chair: Steve O'Brien
ERG: Kleijnen Systematic Reviews
Technical team: Catie Parker, Alex Filby, Ross Dent
Company: Amarin
8 March 2022

Icosapent ethyl (Vazkepa, Amarin)

Marketing authorisation (MHRA)	Indicated to reduce the risk of cardiovascular events in adult statin-treated patients at high cardiovascular risk with elevated triglycerides (≥150 mg/dL [≥ 1.7 mmol/L]) and • established cardiovascular disease, or • diabetes, and at least one other cardiovascular risk factor. Risk factors from SPC: – hypertension or on an antihypertensive medicinal product – age at least 55 years (men) or at least 65 years (women) – low high-density lipoprotein cholesterol levels – smoking – raised high-sensitivity C-reactive protein levels – renal impairment – micro or macroalbuminuria – retinopathy – reduced ankle brachial index
Mechanism of action	Not fully understood, but appears to modulate atherosclerosis pathway by lipid and non-lipid effects
Administration	Oral
Price	Proposed new list price £[redacted] per pack of 120 capsules (£[redacted] per year). No Patient Access Scheme

mg/dL, milligram per decilitre; MHRA, Medicines and Healthcare products Regulatory Agency; mmol/L, millimole per litre; SPC, summary of product characteristics

Summary

Comparators	Best supportive care = stable dose of statins with or without ezetimibe
Clinical setting	Primary care
Subgroups	• **Secondary prevention** (CV1): Adults with established cardiovascular disease • **Primary prevention** (CV2): Adults with diabetes and at least 1 other risk factor
REDUCE-IT clinical trial	Randomised controlled trial comparing icosapent ethyl with placebo (mineral oil)
Model	Partitioned survival approach with 8 health states

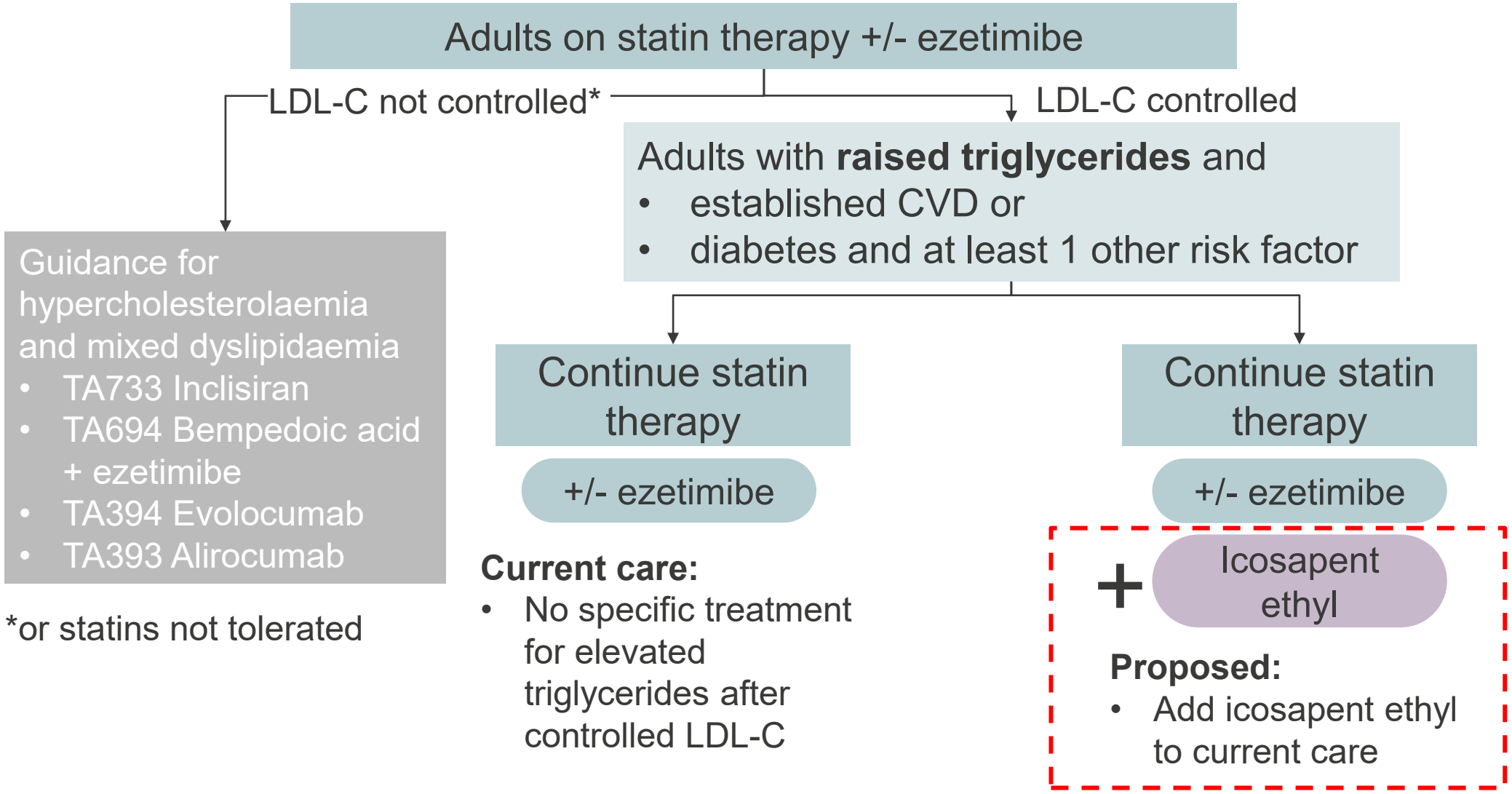
Analyses after first committee meeting only provided for **secondary prevention population**

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Equality and equity considerations

- People with Black, Asian and minority ethnic family backgrounds have higher triglyceride levels and increased CVD risk factors
- People in England's most deprived areas are almost 4 times more likely to die prematurely from CVD than people in the least deprived areas
- Variation in access to secondary and tertiary care
- People with severe mental illness are more likely to develop and die from preventable conditions like CVD
- People with learning disabilities are at increased risk of developing CVD
- Some faiths and ethical beliefs may restrict use of fish products
- Pregnancy and breast-feeding

Treatment pathway & proposed position



- Controlled LDL-C levels (REDUCE-IT): > 1.04 mmol/L and ≤ 2.60 mmol/L
- Raised triglycerides (marketing authorisation): ≥ 1.70 mmol/L

CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; mmol/L, millimoles per litre

REDUCE-IT overview

Randomised, double-blind, placebo-controlled phase 3 trial

Population

N=8,179: No UK participants
General inclusion criteria:

- **TG** ≥1.53 mmol/L* and <5.64 mmol/L
- **LDL-C** >1.04 mmol/L and ≤2.60 mmol/L
- Stable dose of **statins** with or without ezetimibe

Primary prevention (29%)

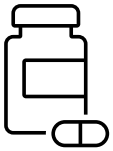
- Adults 50 or older
- Diabetes mellitus
- At least 1 other cardiovascular risk factor†

Secondary prevention (71%)

- Adults 45 or older
- Established CVD

Treatment

Icosapent ethyl
(4g per day)
n=4,089



Placebo
(mineral oil)
n=4,090

Endpoint

Primary: Time from randomisation to first occurrence of 5-point MACE:

- Cardiovascular (CV) death
- Nonfatal myocardial infarction (MI)
- Nonfatal stroke
- Coronary revascularisation
- Unstable angina

Secondary: Time from randomisation to first occurrence of composite of CV death, nonfatal MI, or nonfatal stroke

Median follow up: 4.9 years

*10% variability (1.69 mmol/L) & in 2013 changed to ≥ 2.26 mmol/L, †including older age, cigarette smoking, hypertension, HDL-C ≤1.04 mmol/L, renal disfunction (full list, slide 7)

CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; mmol/L, millimoles per litre; TG, triglyceride

REDUCE-IT results, secondary prevention

Event	Rate ratio or hazard ratio
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

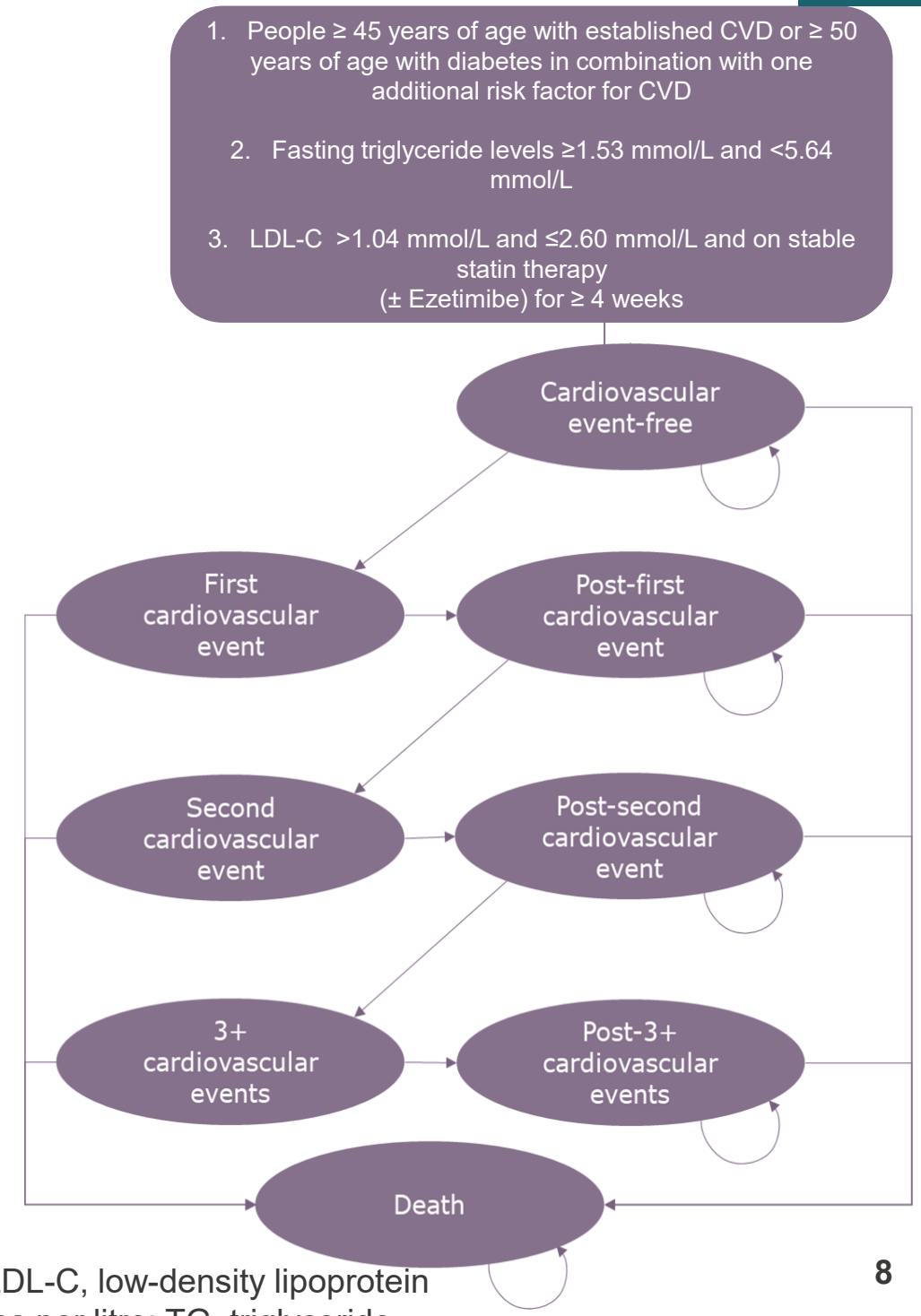
1st event 2nd event 3rd event 4th event

NICE

CI, confidence interval; HR, hazard ratio; RR, rate ratio

Company's model

- Health state cohort model (partitioned survival approach)
- 8 health states based on occurrence of cardiovascular events and death
- 1 day cycle length, 36 year horizon
- Mean age at baseline: 64 years
- Percent male at baseline: 78%
- REDUCE-IT used to estimate parametric survival models for health state occupancy
  - Estimated using composite end points and subdivided between event types
    - Cardiovascular death
    - Myocardial infarction
    - Stroke
    - Unstable angina
    - Revascularisation



CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; mmol/L, millimoles per litre; TG, triglyceride

Key issues

Model driver | Unknown impact | Small impact

	Issue description	Questions	Impact
1	Mineral oil placebo in REDUCE-IT	Should icosapent ethyl be modelled as less effective because of the mineral oil placebo in REDUCE-IT? Scenarios for 0.3 to 13%	
2	Assumption of no treatment waning	Is a 5, 10, 20 year, or no waning assumption most appropriate?	
3	REDUCE-IT population narrower than scope	Can recommendations be made in line with full marketing authorisation (age, LDL-C)?	
4	MACE composite outcome	Is the composite 5-point MACE outcome appropriate to use in the model?	
5	REDUCE-IT generalisability	Are the results from REDUCE-IT generalisable to the NHS in England?	
6	Model structure	Is the company's partitioned survival model approach appropriate for decision making?	N/A

Partially resolved/for brief discussion | Unresolved, for discussion

LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event

Resolved issues

Resolved

Model driver | Unknown impact | Small impact

Issue	Technical engagement	Impact
Time to determine stable statin dose	Time to determine stable dose of statins in REDUCE-IT likely similar to clinical practice	
Complete Kaplan-Meier	Company used full dataset	
Time to event analysis	Company provided full analysis for secondary prevention. ERG agrees	
Non-CV related death HR	Company/ERG use treatment independent	
Utility values	ERG agrees that Stevanovic & O'Reilly baseline values and CG181 multipliers are likely appropriate	
Event costs not adjusted for time since previous event	Company updated event costs to reflect cost per day after event instead of one-off event cost. ERG satisfied with company's changes	
Model validation	Company provided validation checklists: AdViSHE and TECH-VER. ERG satisfied with model validation	
Time to treatment discontinuation	Full TTE analysis provided after ACD. Weibull best statistical fit. Scenario with second best fit - no major impact on ICER	

ACD, appraisal consultation document; CV, cardiovascular; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; TTE, time to event

Consultation responses

- Comments received from
  - Amarin (company)
  - HEART UK
  - EPA Drug Initiative
  - Member of the public

Public and patient organisation consultation comments summary

- Interpretation of evidence regarding mineral oil is not reasonable
- Regulators concluded icosapent ethyl still associated with substantial risk reduction
  - FDA concluded ‘no strong evidence for biological activity of the mineral oil placebo was found by the REDUCE-IT cardiovascular outcomes trial’
- Drugs in STRENGTH and REDUCE-IT are not ‘similar’
- Analysis by European Heart Journal of 80 studies with mineral oil placebo found no consistent pattern of changes in lipid levels or inflammatory markers
- Large economic and health burden of cardiovascular disease in the UK, unmet need
- “Fishy burps do not appear to be a problem for the majority of people. This uncommon side effect is not as bad as having a heart attack or stroke!”

Issue 1: REDUCE-IT & mineral oil placebo (1/3)

Issue background

- Professional organisation & NHSE noted mineral oil placebo and STRENGTH trial results increased uncertainty around REDUCE-IT
- Committee wanted to see scenarios: icosapent ethyl treatment effect reduced by 7% and 13% per Doi et al. 2021 (next slide)

Company ACD response

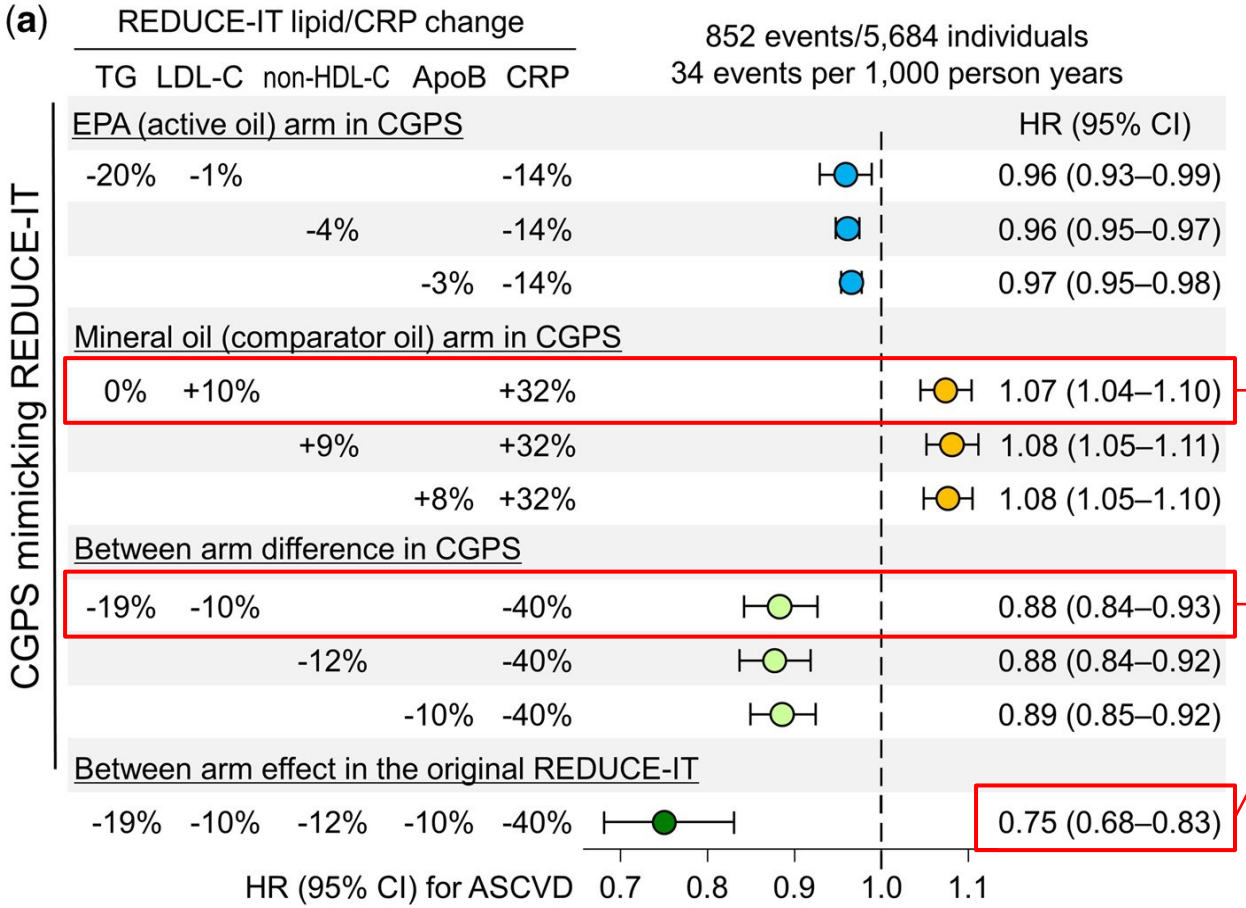
- EMA & FDA concluded putative negative effect of mineral oil should not account for more than 0.3 to 3% of 5-point MACE
- The proposed 7 to 13% reduction in treatment effect based on one Danish observational study that was criticised by the ERG → company consider range implausible
- STRENGTH & REDUCE-IT trials had differences:

	Active treatment	% in secondary prevention
REDUCE-IT	4g/day ≥96% pure EPA ethyl ester	71%
STRENGTH	4g/day of omega-3-carboxylic acids with at least 850 mg of polyunsaturated fatty acids, including EPA and DHA	56%

DHA, docosahexaenoic acid; EMA, European Medicines Agency; EPA, eicosapentaenoic acid; FDA, Food and Drug Administration; NHSE, NHS England; MACE, major adverse cardiovascular event

Issue 1: REDUCE-IT & mineral oil placebo (2/3)

Rationale for exploring 7% & 13% scenarios



HR from mimicking REDUCE-IT (**1.07**) - null value (**1**)
= **7%** additional risk in mineral oil group

HR from mimicking REDUCE-IT (**0.88**) - HR observed in REDUCE-IT (**0.75**)
= **13%** unexplained risk reduction

Source: Doi et al. 2021

NICE

ApoB, Apolipoprotein B; CGPS, Copenhagen General Population Study; CI, confidence interval; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; TG, triglyceride

Issue 1: REDUCE-IT & mineral oil placebo (3/3)

Company ACD response (cont.)

- Mineral oil considered an issue because of small increases in parameters associated with cardiovascular risk in placebo arm of REDUCE-IT
  - Changes could be natural course of disease, or variability and regression to the mean effects, or a negative effect of mineral oil
  - Analysis of cohorts from 2003 to 2019 showed 79% of studies reported LDL-C increases after statin stabilisation similar to placebo arm of REDUCE-IT (slide 28)

REDUCE-IT	Icosapent ethyl			Placebo		
	Baseline (mg/dL)	1 Year (mg/dL)	Change* (mg/dL)	Baseline (mg/dL)	1 Year (mg/dL)	Change* (mg/dL)
TGs	216.5	[redacted]	[redacted]	216.0	[redacted]	[redacted]
Non-HDL-C	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LDL-C	74.0	[redacted]	[redacted]	76.0	[redacted]	[redacted]
apoB†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
hsCRP†	2.2	[redacted]	[redacted]	2.1	[redacted]	[redacted]

*Median change
†Baseline to Year 2

ERG

- No additional evidence presented to inform estimated decrease in treatment effect
- ERG has some reservations, but it is reasonable to consider 7 & 13% reduction scenarios

Should icosapent ethyl be modelled as less effective because of the mineral oil placebo in REDUCE-IT? Scenarios for 0.3 to 13%

apoB, Apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; mg/dl, milligram per decilitre; TG, triglyceride

Issue 2: Treatment waning

Issue background

- Company model assumes no treatment waning
- ERG base case: 10-year post trial applied to 1st, 2nd and 3rd + events
- Committee would have preferred a method linking treatment effect and discontinuation by changing the hazard ratio to 1 at an appropriate time after people stopped icosapent ethyl

Company ACD response

- Efficacy lost due to discontinuation is accounted for in the trial's clinical efficacy curves
- Kaplan-Meier event curves for primary efficacy 5-point MACE composite endpoint, showed treatment effect increases over time before stabilising
- No waning in similar appraisals: TA393, TA394, TA733
- Waning scenarios likely underestimate efficacy observed in people who stop treatment
- Scenarios are limited → assuming patients who discontinue follow placebo efficacy means **all** events that were avoided suddenly occur on discontinuation → not plausible

ACD: In recent TA694, company's model assumed results at 12 weeks were maintained for the duration of time horizon, or until treatment was stopped

ERG

- To compare to similar appraisals, need to consider discontinuation and treatment effects
- Company didn't provide % who would experience multiple events on discontinuation
- Alternative scenario: patients move to placebo effectiveness at end of trial follow-up
- Still uncertain, base case is 10 year waning → no waning can be lower bound to ICER

Is a 5, 10, 20 year, or no waning assumption most appropriate?

ICER, incremental cost-effectiveness ratio; MACE, major adverse cardiovascular event

Issue 3: Eligible population

ACD: acceptable to use LDL-C from REDUCE-IT. Restricting by age may be equality issue

Summary: Marketing authorisation does not specify **age** or **LDL-C level**

REDUCE-IT included people:

- **≥ 45yrs** with CVD
- **≥ 50yrs** with diabetes and at least 1 other risk factor

REDUCE-IT included people with:

- LDL-C >1.04mmol/L and ≤ 2.60mmol/L

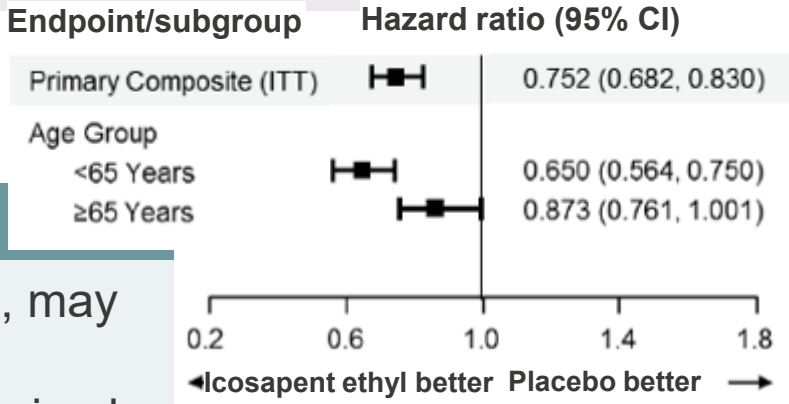
Marketing authorisation:
"to reduce the risk of cardiovascular events in adult statin-treated patients at high cardiovascular risk with elevated triglycerides (≥150 mg/dL [≥ 1.7 mmol/l]) and established cardiovascular disease, or diabetes, and at least one other cardiovascular risk factor"

Company TE response

Population should follow REDUCE-IT, which is narrower than licensed indication

ERG

Subgroup analysis age may effect outcome



Clinical expert comments

- No biological reason to restrict drug to people over 45, may disadvantage people at risk
- Some people in NHS < 45 with CVD or diabetes and raised triglycerides especially in people with South Asian family backgrounds

Can recommendations be made in line with full marketing authorisation (age, LDL-C)?

ACD; appraisal consultation document; CI, confidence interval; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; mmol/L, millimoles per litre; yrs, years

Issue 4: Composite MACE outcome (1/3)

Issue background

- REDUCE-IT had composite 5-point major adverse cardiovascular event (MACE) outcome
- **ERG**: composite outcomes may mask treatment effect of individual outcomes. Should explore impact of single outcomes
- **ACD**: Committee concluded composite 5-point MACE increases uncertainty. Wanted to see Kaplan–Meier curves and hazard ratios for each individual cardiovascular event

Company ACD response

- Icosapent ethyl showed a decreased incidence rate, sustained over time, for each of the individual endpoints included in the 5-point MACE compared to placebo

[redacted]

CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event; n, number

Issue 4: Composite MACE outcome (2/3)

KM curves for individual events & composite MACE in secondary prevention population

Cardiovascular death | Non-fatal myocardial infarction | Non-fatal stroke

[redacted]

ERG: lag in curve separation for these events might mean the composite outcome could bias the size of effect in favour of icosapent ethyl in first 1 to 2 years of treatment

Unstable angina | Coronary revascularisation | 5-point MACE

[redacted]

HR, hazard ratio; KM, Kaplan Meier; MACE, major adverse cardiovascular event

Issue 4: Composite MACE outcome (3/3)

Hazard ratios over time for individual events in secondary prevention population

Cardiovascular death

Non-fatal myocardial infarction

Non-fatal stroke

Unstable angina

Coronary revascularisation

Is the composite 5-point MACE outcome appropriate to use in the model?

CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event

Issue 5: REDUCE-IT generalisability

Issue background

- REDUCE-IT had no UK participants
- Company: comparison of characteristics from REDUCE-IT and retrospective cross-sectional UK study (Steen et al.) shows REDUCE-IT population is similar
- NHSE: concerned trial doesn't reflect current CVD and diabetes management in NHS
- Committee concluded trial's generalisability uncertain

Company ACD response

- In secondary prevention, BMI and systolic BP similar in REDUCE-IT and Steen et al., but differences in age, % male, % with ACS, CHD, diabetes, hypertension, or CHF
- 2 observational studies in France & Canada had similar residual CV risk as REDUCE-IT
- Recent UK census: 84.8% 'Caucasian' → similar to 90.3% 'white race' in REDUCE-IT
- Benefit of icosapent ethyl on 5-point MACE similar by ethnicity: white HR 0.77, 95% CI 0.69-0.85; non-white HR 0.60, 95% CI 0.43-0.83
- SGLT2 inhibitors ([redacted]) & GLP-1 agonists ([redacted]) use in REDUCE-IT consistent with period of trial. PCSK9 inhibitors were exclusion criterion

ERG

- French & Canadian studies do not add evidence for NHS in England
- If PCSK9 inhibitors reduce rate of cardiovascular events, this would likely impact icosapent ethyl treatment effect → impact may be small if PCSK9 inhibitor use is low

Are the results from REDUCE-IT generalisable to the NHS in England?

ACS; acute coronary syndrome; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CHF, congestive heart failure; CI, confidence interval; CVD; cardiovascular disease; GLP-1, glucagon-like peptide-1; HR, hazard ratio; MACE, major adverse cardiovascular event; PCSK-9, proprotein convertase subtilisin/kexin type 9; SGLT2, sodium-glucose cotransporter-2

Issue 6: Model structure

Issue background

- Company's model different than models for similar appraisals: TA393, TA394, TA420
- ERG: unclear appropriateness of partitioned survival approach because it assumes independence of endpoints
- **ACD:** Committee concluded model structure was uncertain

Company ACD response

- To align with REDUCE-IT, time to event endpoints modelled so people progress in a specific order through health states & cannot skip or return to a previous state
- Model uses time from randomisation to a 1st, 2nd or 3rd + event, so no issues surrounding a crossover of the 1st, 2nd or 3rd + event endpoints reported during the trial period
- Beyond trial period, extrapolations used for the 1st, 2nd or 3rd + event curves. Curves that crossed over previous event curve were disregarded and considered clinically implausible

ERG

No additional justification provided for model structure

Is the company's partitioned survival approach appropriate for decision making?

Other considerations

Innovation

- Clinical experts: Innovative because it appears to work on a pathway that is not yet defined and addresses unmet need of people with elevated triglycerides and residual CVD risk

Equality issues

- People with Black, Asian and minority ethnic family backgrounds have higher triglyceride levels
- People in England's most deprived areas are almost 4 times more likely to die prematurely from CVD than people in the least deprived areas
- People with severe mental illness are more likely to develop and die from preventable conditions like CVD
- People with learning disabilities are at increased risk of developing CVD
- Some religions have restrictions on fish products

Are there any equalities issues that need to be taken into account?

CVD, cardiovascular disease

Base case assumptions – secondary prevention population

	Company new base case	ERG
Treatment effect	From REDUCE-IT. No adjustment	From REDUCE-IT. No adjustment
Treatment waning	No waning	Assume at 10 years the comparator hazard ratio applied to people who had discontinued icosapent ethyl at that point
KM data	Complete KM	Complete KM
Extrapolated time to event curves	Per TSD 14, fitted parametric models to data with treatment group as covariate	Per TSD 14, fitted parametric models to data with treatment group as covariate
Non-CV related death HR	Treatment independent	Treatment independent
Event costs	Applied as daily cost for 60 days post event	Applied as daily cost for 60 days post event
Time to treatment discontinuation	Weibull	Weibull

NICE

CV, cardiovascular; HR, hazard ratio; KM, Kaplan-Meier; TSD, Technical Support Document

Deterministic cost-effectiveness results

Secondary prevention (CV1)

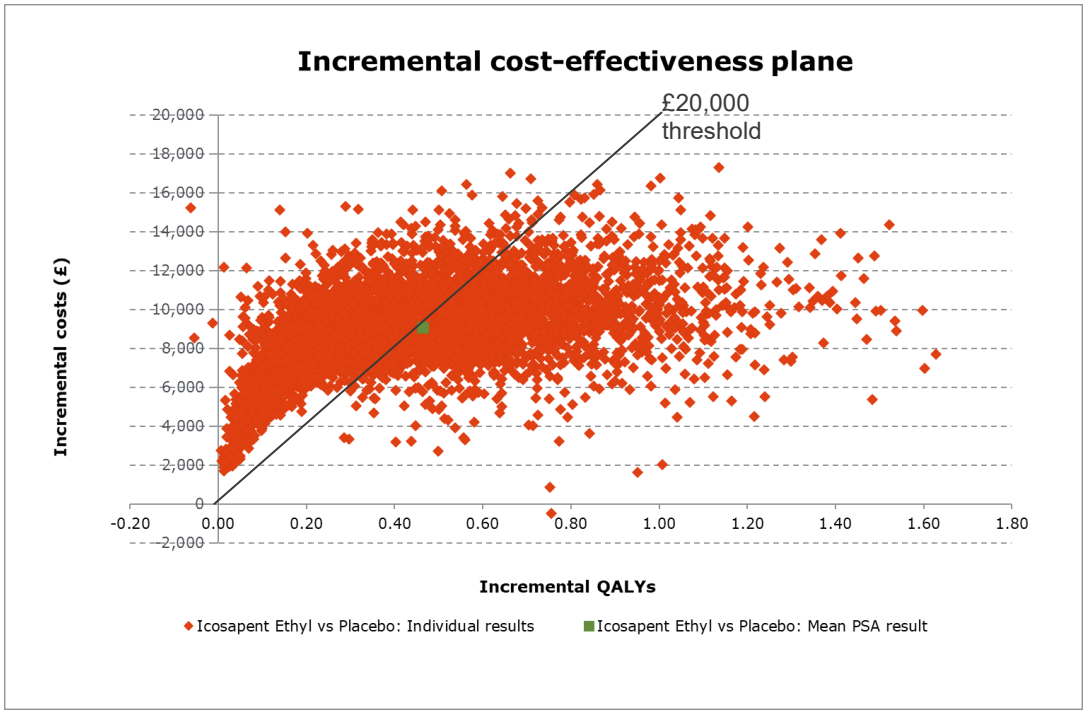
Scenario	Incremental cost	Incremental QALYs	ICER (£/QALY)
Company base case*	**£9,723**	**0.490**	**19,848**
Treatment effect reduced by 0.3%	XXXX	XXXX	20,157
Treatment effect reduced by 1%	XXXX	XXXX	20,908
Treatment effect reduced by 2%	XXXX	XXXX	22,063
Treatment effect reduced by 3%	XXXX	XXXX	23,325
Treatment effect reduced by 7% (ERG)	XXXX	XXXX	29,832
Waning upon discontinuation at 20 years**	XXXX	XXXX	20,098
ERG base case: waning upon discontinuation at 10 years**	**£9,892**	**0.438**	**22,609**
Treatment effect reduced by 7%	XXXX	XXXX	34,067
Treatment effect reduced by 13%	XXXX	XXXX	55,465
Waning upon discontinuation at 5 years**	XXXX	XXXX	26,228

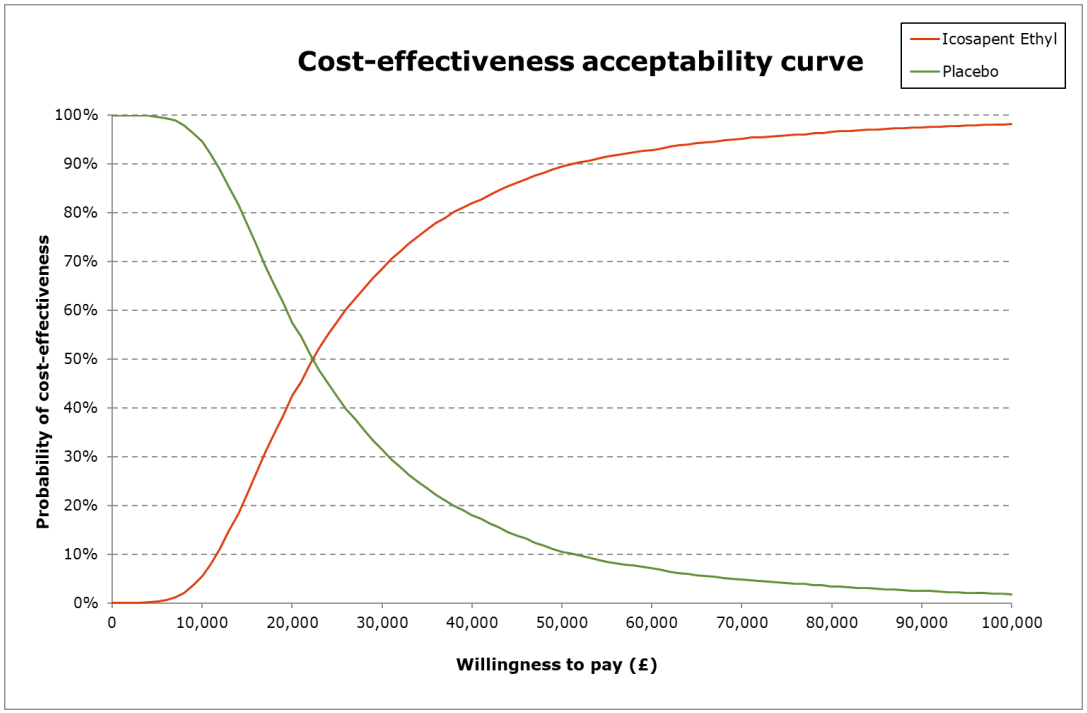
*Probabilistic: £19,625/QALY. ** issues with plausibility of waning scenarios (slide 16). Scenarios do not link treatment effect and discontinuation (committee preference in ACD)

ACD, appraisal consultation document; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TTD, time to treatment discontinuation

Cost-effectiveness results

Company base case





NICE

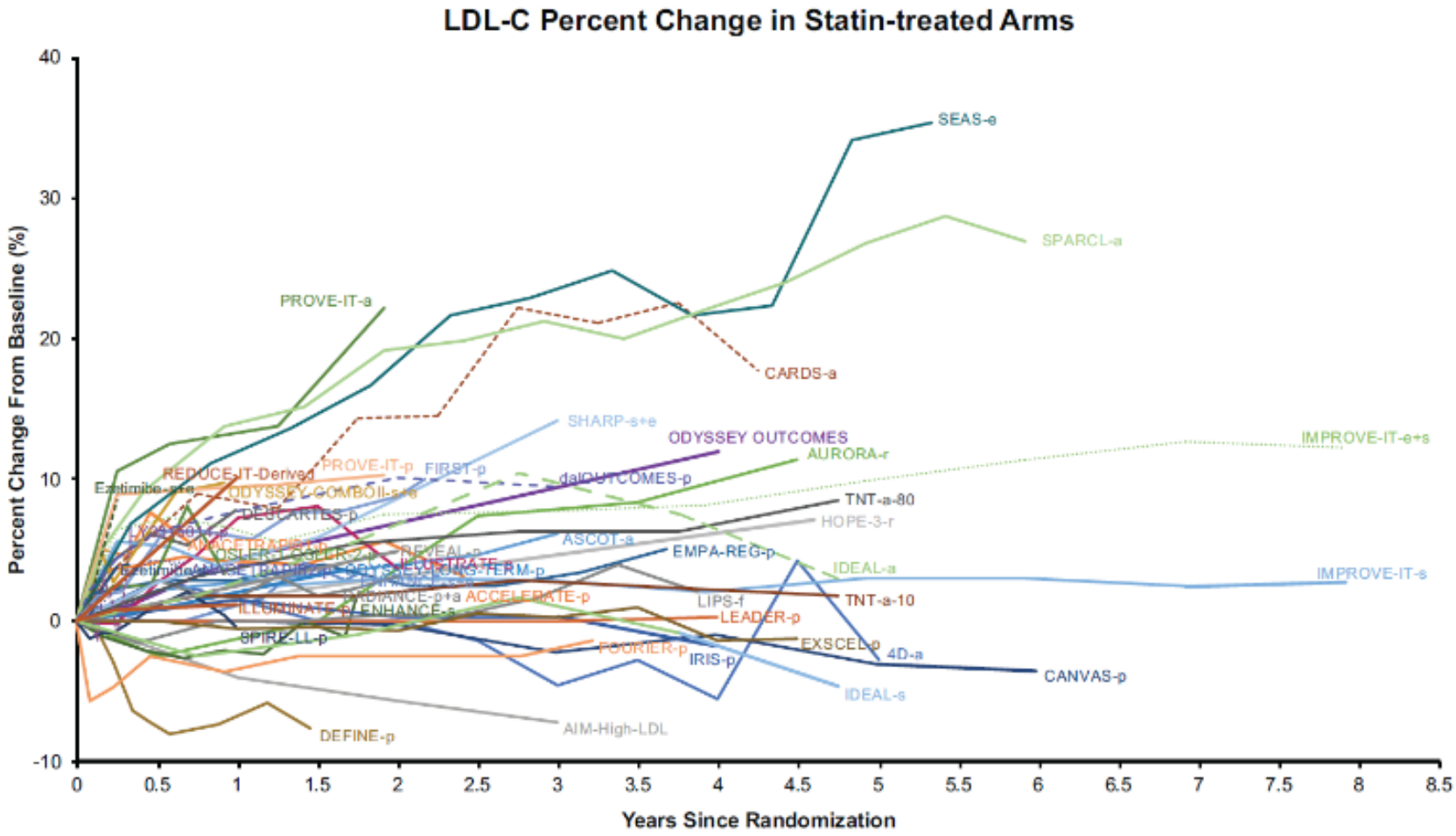
PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year

Back up slides

Issue 1: REDUCE-IT & mineral oil placebo

Company ACD response

Analysis of cohorts from 2003 to 2019 showed 79% of studies reported LDL-C increases after statin stabilisation similar to placebo arm of REDUCE-IT



LDL-C, low-density lipoprotein cholesterol